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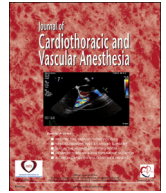
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Original Article

Transfusion Threshold of Hemoglobin 80 g/L Is Comparable to 100 g/L in Terms of Bleeding in Cardiac Surgery: A Prospective Randomized Study



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Objective: Anemia is common after cardiac surgery and, according to some suggestive evidence, may be associated with increased bleeding, other morbidity, and mortality. However, transfusion of red blood cells (RBC) may cause adverse effects and increase cost. The authors hypothesized that the restrictive hemoglobin threshold (Hb of 80 g/L) may aggravate bleeding more than the higher Hb threshold (Hb 100 g/L).

Design: Prospective randomized trial.

Type of Hospital: University Hospital of Helsinki, Finland.

Participants: Eighty patients with written informed consent, scheduled for elective open-heart surgery were randomized in 2 groups.

Interventions: Two study groups had RBC transfusion threshold of either Hb 80 g/L or 100 g/L. These triggers were followed for a 24-hour period postoperatively. A medical follow-up was carried out for 7 days after surgery.

Measurements and Main Results: Rotational thromboelastometry (ROTEM) and conventional laboratory tests were performed to evaluate coagulation. There was no significant difference in bleeding or ROTEM parameters between the groups. Complication rate and Hb concentration after 7-day follow-up were not different between the groups, but Group 100 g/L had received twice the amount of RBC transfusions.

Conclusion: Hb threshold of 80 g/L for RBC transfusion in cardiac surgery is comparable to 100 g/L in terms of bleeding and possibly short-term complications.

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Key Words: cardiac surgery; transfusion, bleeding

HEMOGLOBIN (Hb) has a crucial role in carrying oxygen to tissues. Evidence supports that red blood cells (RBCs) play an active role in hemostasis.¹ Anemia is common during and

after cardiac surgery, and it is associated with increases in morbidity and mortality.^{2–4} Transfusion of allogeneic RBC is typically the treatment of choice. Cardiac surgery has one of the highest associated transfusion rates with over 50% of patients receiving transfusions.⁵ On the other hand, transfusion of RBC, or other blood components, is associated with numerous harmful effects, such as infection, acute kidney injury, ischemic events, prolonged hospital stay, increased early and late mortality, and hospital costs.^{2,6–8}

A recent guideline from the AABB recommends restrictive transfusion strategy in most clinical settings, including cardiac surgery.⁹ The results of trials studying critically ill patients (ie, TRICC [Transfusion Requirements in Critical Care] or TRISS

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[Transfusion Requirements in Septic Shock]) also support the idea of lower transfusion thresholds because there was no significant difference in 30- and 90-day mortality when comparing higher (Hb 90 g/L) versus lower (Hb 70 g/L) transfusion thresholds.^{10,11} However, particularly in cardiac surgery,^{12–14} recent studies have conflicting results regarding restrictive transfusion strategies, and no clear consensus exists. Transfusion thresholds in cardiac surgery have generally been more liberal in clinical practice, partly due to justified concern of cardiac ischemia, bleeding, and other undesired sequelae.

It has been shown that lower hematocrit (Hct) influences coagulation *in vivo*.¹⁵ Rotational thromboelastometry (ROTEM), a point-of-care whole blood coagulation test, gives more rapid and detailed information about patients' coagulation status, compared with conventional laboratory tests performed with cell free plasma.^{16,17} The use of ROTEM-guided transfusion protocols also has been shown to reduce the need for transfusions in cardiac surgery.¹⁸

The aim of this prospective randomized study was to compare the effect of 2 different RBC transfusion thresholds (80 g/L v 100 g/L) perioperatively on bleeding and coagulation parameters measured by ROTEM in cardiac surgical patients.

Methods

After registering the study at the Hospital District of Helsinki and Uusimaa (§94,9.05.2014) and receiving approval from the institutional Ethics Committee for Surgery in Helsinki University Hospital 2014 (D-number 58/13/03/02/2014), the authors gathered 80 patients scheduled for non-emergency coronary artery bypass grafting (CABG), simple one valve (aortic or mitral) replacement or both, requiring cardiopulmonary bypass (CPB). Patients were operated on between June 2014 and December 2015. Exclusion criteria included any hereditary or acquired hemostatic disorders, any malignancies, and severe chronic kidney disease (glomerular filtration rate < 30 mL/min). Patients' medical history and severity of the surgery was described with European System for Cardiac Operative Risk Evaluation, (numeric) EuroSCORE I.¹⁹ After providing written informed consent, patients were randomized in 2 groups: (1) "Group 80," RBC transfusion threshold of 80 g/L, and (2) "Group 100," RBC transfusion threshold of 100 g/L. Randomization was done in blocks of 20 patients and using closed envelopes (Fig 5). Use of other blood components and medications was left to clinicians' discretion and based on Helsinki University Hospital treatment protocols; that is, if postoperative bleeding is severe (> 200 mL/h), activated coagulation time (ACT, s), thromboplastin time value (TT, %), and platelet count (PLC) are measured. If ACT is prolonged more than 10 seconds compared with pre-bypass level, 25 mg of protamine is administered. Pooled human plasma (5 mL/kg) is given if TT is < 50% and platelets (1 U/10 kg) transfused if PLC is < 50 × 10⁹/L. If bleeding continues, 1 g of tranexamic acid is administered. Intervention started at the beginning of surgery, and it lasted

24 hours. The study was unblinded due to the Finnish practice of anesthetists performing transfusions themselves.

Patients' own medication was continued until surgery according to hospital protocol. Patients did not receive any low molecular weight heparin for 24 hours before surgery. The possible acetylsalicylic acid treatment was continued until surgery, but the cessation of oral anticoagulation was performed according to the hospital protocol: Warfarin 3 days and new oral anticoagulants 5 days preoperatively. Patients received a 1-g bolus of tranexamic acid during anesthesia induction. CPB was performed according to institutional standards described elsewhere.²⁰ Before cannulation a bolus of heparin (300–400 IU/kg body weight) was administered. Another 1 to 2 g bolus of tranexamic acid also was administered in the CPB routinely. Intraoperatively ACT was measured repeatedly to monitor the efficiency of anticoagulation. In the case of ACT < 480 s, a further bolus of heparin was administered. After finishing the CPB, heparin was antagonized with protamine sulfate administered at 1 mg to 100 IU ratio to initial dose of heparin.

Conventional laboratory tests were performed preoperatively and at predetermined time intervals. During surgery and postoperative intensive care, Hb concentrations were monitored hourly during surgery, every 30 minutes during CPB, and every 2 to 3 hours in the intensive care unit (ICU), or more frequently, if needed. If Hb level was 79 g/L or less, 99 g/L or less, respectively, the patient received 1 unit of packed RBC, and Hb was measured again. Transfusions were carried out until Hb level reached 80 g/L or more, 100 g/L or more, respectively. Cell salvage was used only in few isolated cases, as procedures were estimated to be simple and patients did not have predisposing risk factors for extensive bleeding.

ROTEM (TEM International GmbH, Munich, Germany) was performed at 3 predetermined time points: before anesthesia induction, immediately after CPB/surgery, and on the first postoperative morning. Tissue factor with (FibTEM) or without (ExTEM) cytochalasin D was used for coagulation activation. In FibTEM, platelet function is inhibited completely, therefore it is possible to measure the isolated effect of fibrinogen on blood coagulation. The following variables were recorded: clotting time (CT, s), clot formation time (CFT, s), maximum rise in clot firmness (given as the angle α), maximum clot firmness (MCF, mm), and clot lysis after 30 minutes. The clinical staff was blinded to the ROTEM data. Other data collected during the study period were the amount of bleeding during the surgery (estimate done by surgeons/anesthetists) and postoperatively from the chest tubes, RBC and blood product transfusions, diuresis, and cumulative fluid balance. Patient data during the surgery and intensive care were collected with PI Client Information System (Caresuite 8.2, PiCIS Inc, San Francisco, CA).

Statistical Analysis

Based on results of the authors' previous study,²¹ the group size was calculated with power $(1-\beta) = 80\%$ and $\alpha = 0.05$

assuming that Group 100 would have 25% less bleeding than Group 80.

The differences were analyzed with the nonparametric repeated measures analysis of variance (Kruskal-Wallis test). Correlations were tested with the Spearman test. Mann-Whitney U test was used for paired comparisons. Because the data was mostly not normally distributed (Kolmogorov-Smirnov test), results are shown as medians (interquartile range, IQR). The results of normally distributed parameters are shown as mean values with 95% confidence intervals (CIs). Significance is developed at p values less than 0.05. Statistical analysis was performed with SPSS 22.0 for MAC (SPSS Inc, Chicago, IL).

Results

Eighty non-emergency cardiac surgery patients were included in the study; 40 patients were randomized in each group. All 80 patients were included in the analyses. Characteristics of the patients were fairly similar between the both groups, with the exception of the patients in Group 80 being older ($70.5 \nu 64.5$, $p = 0.023$) and having a higher EuroSCORE ($6.13 \nu 4.30$, $p = 0.007$) (Table 1).

In the Group 80, mean Hb (95% CI) concentration right after initiating CPB was 88.9 g/L (83.5–94.3 g/L) and after weaning from CPB 98.4 g/L (94.8–102.1 g/L). In the Group 100, Hb after initiating CPB was 90.7 g/L (86.8–94.5 g/L) and after weaning from CPB 106.4 g/L (104.3–108.4 g/L). Although no statistically significant difference between the groups in mean Hb was observed before surgery, it developed into statistical significance during CPB (see Fig 1). Difference between the groups remained statistically significant until the first postoperative day (POD). Seven days after surgery there was no difference in the Hb values between the groups

(100 g/L ν 104 g/L, $p = 0.722$). In both groups, Hb values preoperatively were significantly higher than in the operating room (OR), ICU, or 7 days postoperatively ($p < 0.001$). Thirty-five percent of patients in Group 80 had at least 1 Hb measurement under 80 g/L during the entire CPB, 84% of patients in Group 100 had at least 1 Hb measurement under 100 g/L, respectively. After CPB, numbers were 6% and 16%, respectively (Table 4).

Between study groups, there was no significant difference in intraoperative or postoperative bleeding. In Group 80, mean (95% CI) blood loss in the OR was 433 mL (356–510 mL) and in the ICU 680 mL (551–808 mL). In Group 100, the blood loss was 427 mL (95% CI 365–489 mL) in the OR and 618 mL (95% CI 532–703 mL) in the ICU. Patients in Group 100 were given significantly more RBC transfusions in the OR ($2.0 \text{ U} \nu 0.9 \text{ U}$, $p = 0.001$), but not in the ICU ($0.3 \nu 0.4 \text{ U}$, $p = 0.542$). Amount of other transfused blood products (pooled human plasma or platelets) showed no significant differences between the groups, $p > 0.05$. Finnish RBC unit equals approximately 250 mL, pooled human plasma unit 200 mL and platelet unit 200 mL.

Mean ROTEM parameters were within normal ranges in both groups during the entire study period. The MCF, CT, CFT, and α -angle in ExTEM and FibTEM showed no significant differences between the groups. No excessive lysis of the clot was observed in any of the cases (Figs 2–4).

Preoperative conventional laboratory results showed no signs of hyper- or hypocoagulation, median values were in the reference range (Table 2). There were no significant differences in these analyses between the groups.

Preoperative PLC was positively correlated with preoperative ExTEM ($p < 0.001$) and FibTEM MCF ($p = 0.016$). Preoperative Hct was negatively correlated with preoperative ExTEM ($p < 0.001$) and FibTEM MCF ($p = 0.004$).

Table 1
Background Information

	Group 80	Group 100	p Value
Male, n (%)	29 (72.5)	28 (70.0)	
Female, n (%)	11 (37.5)	12 (30.0)	
Age*	70.5 (67.8–73.2)	64.5 (60.6–68.3)	0.023
BMI, kg/m ²	26.7 (4.8)	28.4 (8.6)	0.245
EuroSCORE I	6 (4)	4 (4)	0.007
Surgery, n (%)			
CABG	28 (70)	29 (72.5)	
CABG + AVR	5 (12.5)	3 (7.5)	
AVR	4 (10)	7 (17.5)	
MVR	1 (2.5)	0 (0)	
Other	2 (5)	1 (2.5)	
Urgent	21 (52.5%)	18 (45%)	
Elective	19 (47.5%)	22 (55%)	
CPB time, min	96.5 (38.3)	96.5 (41.5)	0.912
Ischemia time, min	73.0 (31.3)	76.0 (37.3)	0.996
Days till discharge to secondary ward*	1.88 (1.37–2.38)	1.47 (1.09–1.85)	0.120

Abbreviations: AVR, aortic valve replacement; BMI, body mass index; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; MVR, mitral valve replacement; OR, operating room.

Median values (unless marked * for mean value), interquartile range/95% confidence interval in parentheses.

p Value determined with Mann-Whitney U test.

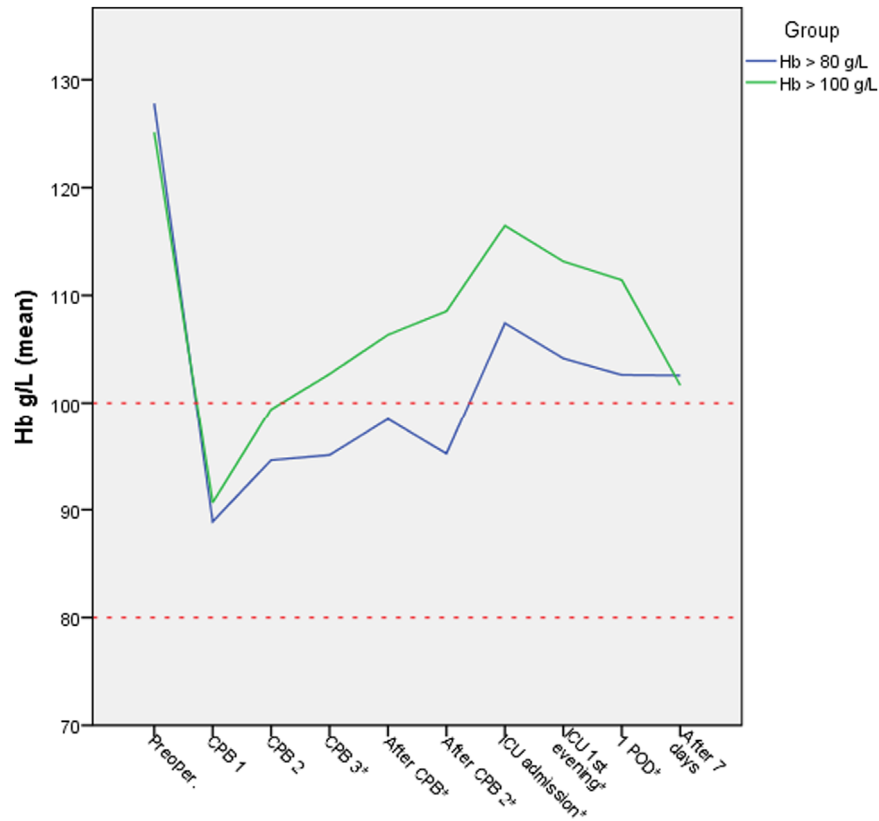


Fig 1. Mean hemoglobin during the study period at various time points. *Statistically significant differences. CPB, cardiopulmonary bypass; ICU, intensive care unit; POD, postoperative day.

Preoperative PLC was associated with the subsequent ROTEM analyses during the perioperative period as well; p values for correlations between preoperative PLC and post-CBP ExTEM

were 0.003, FibTEM 0.002, and POD 1 ExTEM 0.001, FibTEM 0.048. There were no significant ROTEM changes in individual patients during the course of the study period.

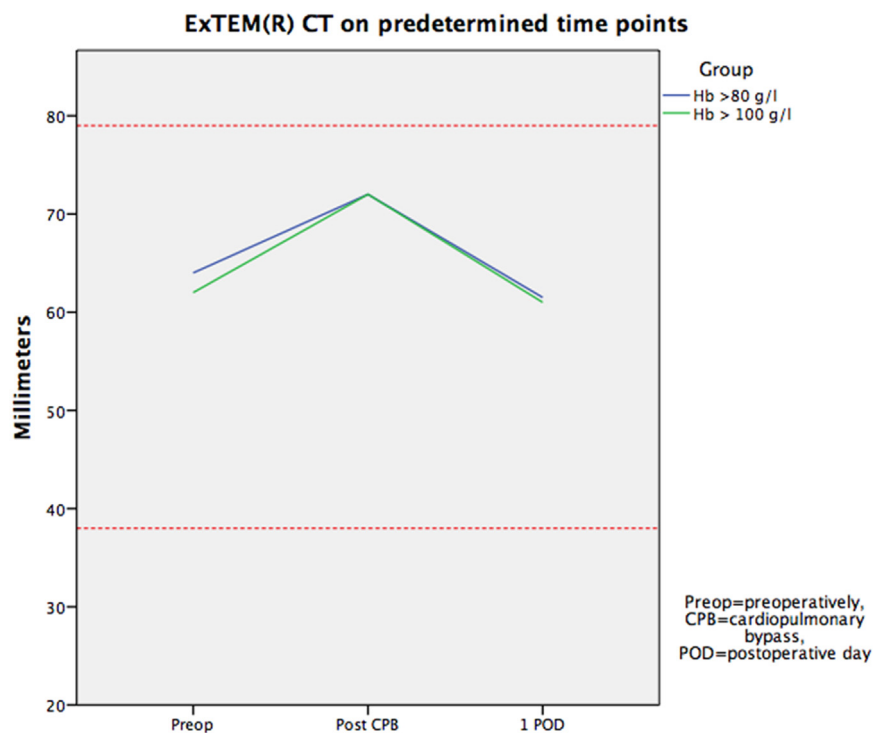


Fig 2. ExTEM clotting time (mean) on predetermined time points. Reference range shown with red lines.

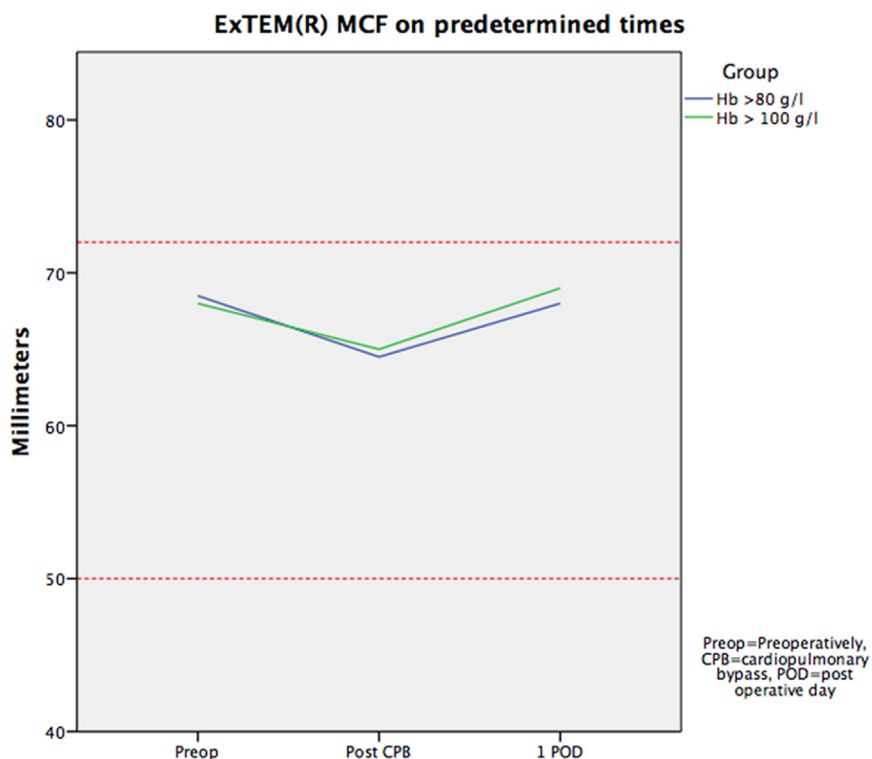


Fig 3. ExTEM maximum clot firmness (mean) on predetermined time points. Red dotted lines represent reference range.

Four re sternotomies due to bleeding were performed during the first 24 hours after surgery on 2 patients in each group. These patients had preoperatively significantly lower Hb (113 ν 135 g/L, $p = 0.004$) and Hct (34.5 ν 40.0, $p < 0.001$) in comparison with other study patients. Their ROTEM-parameters, Hb during surgery and postoperatively, PLC, activated

partial thromboplastin time (aPTT), and TT did not differ significantly from other patients. Only 1 major thrombotic complication was recorded: 1 patient in Group 80 with a CABG operation had postoperative myocardial infarction with ST-elevation. In this particular patient, there was no sign of hypercoagulation in the laboratory analyses. The creatinine

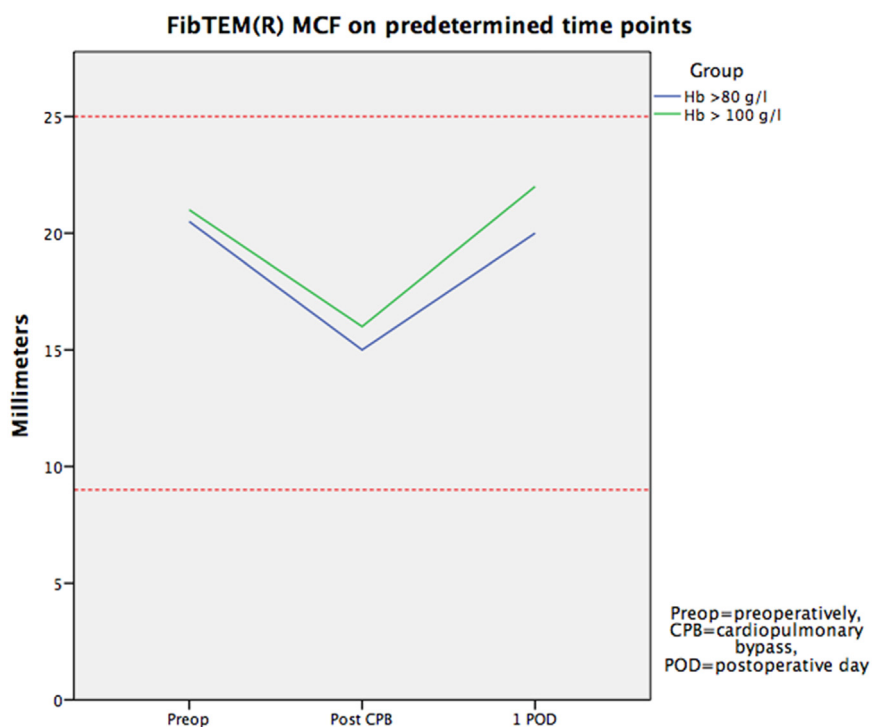


Fig 4. FibTEM maximum clot firmness (mean) on predetermined time points. Red dotted lines represent reference range.

Table 2

Laboratory Tests at Predetermined Time Points During the Study (Preoperative Unless Stated Otherwise)

Lab Test	Ref. Range	Group 80	Group 100	p Value*
Hb (g/L)	(134-167 [men], 117-155 [women])	137 (25)	136.5 (19)	0.600
Hb 1 week	(134-167 [men], 117-155 [women])	100 (20)	104 (16)	0.722
Hct (%)	(35-46 [men], 39-50 [women])	40 (5.5)	40 (5.3)	0.527
PLC ($\times 10^9/L$)	(150-360)	222 (115)	209 (88)	0.829
APTT, s	(23-33)	28 (5)	28 (2)	0.334
TT, n (%)	(70-30)	94 (26)	87 (19)	0.943
INR		1.0 (0.1)	1.1 (0.1)	0.456
Creatinine, mmol/L	(60-100 [men], 50-90 [women])	87 (26)	81 (32)	0.502
Creatinine POD 1	(60-100 [men], 50-90 [women])	82.5 (34)	79.5 (41)	0.411
Creatinine 1 week	(60-100 [men], 50-90 [women])	91.5 (30) [†]	90 (47) [†]	0.248
CK-MBm [‡]	(0-7 $\mu g/L$)	18 (13)	15.5 (11)	0.199

Abbreviations: APTT, activated partial thromboplastin time; CK-MBm, creatinine kinase MB-mass; Hb, hemoglobin; Hct, hematocrit; PLC, platelet count; POD, postoperative day; TT, thromboplastin time.

Values are medians (interquartile range in parentheses).

*p Value determined with Mann-Whitney U test.

[†]Highest measured value during 7-day follow-up.

[‡]CK-MBm on POD 1.

kinase MB-mass (CK-MBm) was only slightly elevated above the reference value of CK-MBm on POD 1 in both groups as values remained under 50 $\mu g/L$ in all except the 1 patient

suffering myocardial infarction with ST-elevation (CK-MBm reaching peak value of 119 $\mu g/L$). The difference in median CK-MBm between groups was not statistically



CONSORT 2010 Flow Diagram

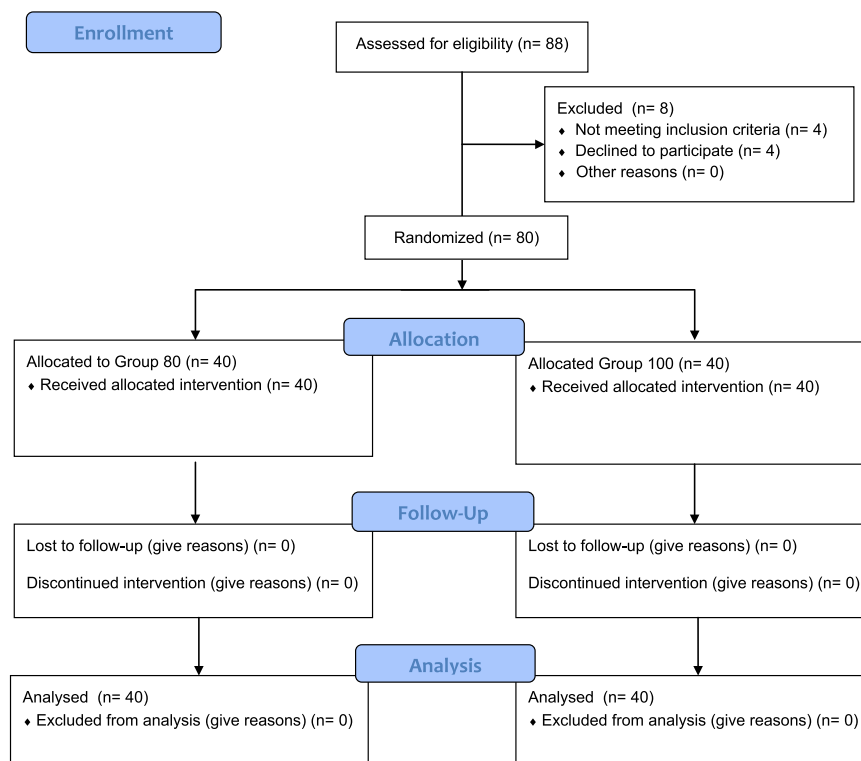


Fig 5. Patient enrollment flow diagram.

Table 3
Transfusions, Bleeding, and Fluid Balance

		Group Hb > 80 g/L	Group Hb > 100 g/L	p Value (t test)
RBC, U	OR	0.90 (0.47–1.33)	1.98 (1.52–2.43)	0.001
	POD 1	0.38 (0.05–0.70)	0.25 (–0.01 to 0.51)	0.542
	7-day	0.45 (0.19–0.71)	0.38 (0.03–0.72)	0.727
Plasma, U	OR	0.18 (–0.07 to 0.42)	0.20 (–0.08 to 0.48)	0.894
	POD 1	0.20 (–0.12 to 0.52)	0.05 (–0.05 to 0.15)	0.367
	7-day	0.03 (–0.03 to 0.08)	0	0.323
Platelets, U	OR	0.80 (–0.13 to 1.73)	1.40 (0.19–2.61)	0.429
	POD 1	1.20 (0.07–2.33)	0.90 (–0.16 to 1.96)	0.697
	7-day	0	0	
Albumin, g	OR	12.5 (5.63–19.37)	8.0 (1.94–14.06)	0.324
	POD 1	21.10 (16.04–26.16)	17.50 (11.63–23.37)	0.350
Bleeding, mL	OR	433.3 (356.6–510.1)	427.1 (365.3–488.9)	0.899
	POD 1	679.6 (551–808.5)	618.0 (532.8–703.2)	0.422
Fluid balance, mL	POD 1	3,948.4 (3,509.0–4,387.8)	3,399.2 (–2,839.6 to 3,958.7)	0.123
Diuresis, mL	POD 1	2,035.8 (1,793.0–2,278.6)	2,072.6 (1,843.6–2,301.6)	0.824

Abbreviations: OR, operating room; Plasma, pooled human plasma, Octaplas; RBC, red blood cells; POD, postoperative day; 7-day, week long follow-up. Mean values, 95% CI in parentheses.

significant (17.0 µg/L [IQR 14.0] v 16.0 µg/L [IQR 10.0], $p > 0.05$).

Plasma creatinine values were not significantly different between the groups: preoperatively 88.9 v 87.3 µmol/L ($p = 0.775$), on POD 1 86.9 v 83.2 µmol/L ($p = 0.548$), and the peak value during the 7-day period postoperatively was 105.8 v 96.4 µmol/L ($p = 0.276$). In both groups elevation of creatinine to the peak value was significant ($p = 0.001$ and $p = 0.003$, respectively). The cumulative urine output (2,036 v 2,073 mL) and fluid balance (+3,948 v +3,399 mL) were not significantly different between the groups ($p = 0.824$ and $p = 0.123$, respectively; Table 3).

Discussion

In this study, the authors showed that there was no significant difference in blood loss or blood coagulation related to open cardiac surgery when transfusion threshold was either Hb value of 80 g/L or 100 g/L. The Hct value did not correlate with any of the thromboelastometry or coagulation parameters. Therefore, it seems that higher Hct may not decrease the risk of bleeding or coagulation disturbance in patients undergoing open-heart surgery. This study outcome is

consistent with previous reports and latest guidelines of transfusion thresholds in cardiac surgery patients. The effect of Hb value or RBC transfusion on bleeding or coagulation is unclear. The previous studies have shown variable results in cardiac or general surgery.^{13,14}

The amount of blood loss in the current study was relatively small, and no significant disturbances in coagulation were observed. Although, Group 100 did receive twice the amount of RBCs compared with Group 80 during the first POD, and the mean Hb concentration in both groups remained higher than 100 g/L during the first POD, even with the transfusion thresholds defined as described. Furthermore, patients' pre-operative Hb values were in or close to the normal laboratory reference range, and the relatively small amount of blood loss, as well as accurate perioperative fluid therapy, did not lower the Hb values to reach lower transfusion threshold in numerous cases. Standardized priming volume of 1,000 to 1,500 mL Ringer's Acetate (with 5,000 IU heparin) for the CPB also did not produce clinically significant hemodilution. Finally, the authors' study protocol in Group 100 may increase the treatment costs and predispose patients to transfusion-related adverse effects without any clinical impact on bleeding or coagulation. One week after surgery, the Hb difference between the groups was lost. There was no significant

Table 4
Percentage (%) of Patients in Various Hb Categories During the Study

	CPB			After CPB			ICU first 12 h			POD 1		
	< 80 g/L	80–100 g/L	> 100 g/L	< 80 g/L	80–100 g/L	> 100 g/L	< 80 g/L	80–100 g/L	> 100 g/L	< 80 g/L	80–100 g/L	> 100 g/L
Group 80	35.3	44.1	20.6	5.7	42.9	51.4	0	30.0	70.0	0	47.5	52.5
Group 100	18.9	64.9	16.2	0	16.2	83.8	0	10.0	90.0	0	5.0	95.0

Abbreviations: CPB, cardiopulmonary bypass; ICU, intensive care unit; POD, postoperative day. The time intervals are CPB (during and after), ICU (during first 12 h in the ICU), and POD 1.

difference between transfusions during this 7-day period postoperatively.

Murphy et al reported nonsuperiority of lower Hb threshold,¹³ but the authors were unable to show actual benefits of higher threshold as well. On the other hand, Reeves et al were able to draw the conclusion that cost-wise lower hemoglobin threshold would be superior without causing any additional morbidity.¹⁴ These findings underline the need to further re-evaluate the practices of liberal transfusions.

In this study, ROTEM analysis did not show any significant differences between study groups. Clot formation and clot strength were similar in both groups, which reflects well the fact that clinical tendency to bleed did not differ between the groups. This might be explained by higher than aimed Hb levels. It has been shown before that clot strength reduces when using hydroxyethyl starch (HES)-based colloids,^{21,22} and after abandoning HES solutions in surgical fluid management in the authors' institution, albumin (4% and 20% solutions) is the only choice of colloid. This in addition to the authors' patients' lack of underlying coagulation disturbances ensure proper clotting during perioperative period. Platelet count was associated with more firm clots (higher MCF) in the ROTEM analysis, as expected. FibTEM measures specifically the effect of fibrinogen, RBC, and factor XIII on the clot formation, and positive correlation of platelets with FibTEM MCF might be explained with complex effect of platelets and their mediators in coagulation even without platelet adhesion. It has been shown that platelet blocking with acetylsalicylic acid or clopidogrel does not block the formation of thrombin.²³ It was rather surprising to observe that lower Hct was associated with thicker clots preoperatively in the present study. Similar findings have actually been demonstrated with ROTEM CT-parameter already in vitro by Iselin et al²⁴ and Spiezia et al,²⁵ as well as in vivo with TEG MA-parameter by Roeloffzen et al.¹ In their experimental studies, the observation was speculated to be attributed to the test method itself. In fact, the test in these situations is more sensitive to the total amount of clotting factors rather than the concentration of cell surfaces or manufacturing process and storage of RBC. However, authors assumed that this finding may not have significant clinical relevance.

Patients enrolled in this study were scheduled for non-emergency surgery, but had higher EuroSCORE values than most of the usual elective cardiac surgery patients, in the authors' experience. Data collected previously in the authors' institution showed mean EuroSCORE in 428 non-emergency CABG patients to be 2.2 and in 220 other cardiac surgery patients to be 2.6.²⁶ Patients' mean age was rather high, especially in Group 80 as the difference was statistically significant. Older age is known to predispose to complications and delayed recovery.²⁷ Nevertheless, this group managed as well as did Group 100 regarding measured parameters and complications.

The creatinine concentration behaved as expected with modest rise after surgery and CPB. Urine output remained normal and fluid balance moderately positive throughout the first perioperative day. Lack of differences between groups in

these parameters did not reflect the relative abundance of transfusions in Group 100. Despite that perioperative cardiac ischemia has been a major concern throughout the years and has perhaps led to extensive transfusions during cardiac surgery, this study implies that lower transfusion threshold (80 g/L) might not aggravate the incidence of cardiac ischemia.

One of the strengths of this prospective randomized study is the fair similarity of the preoperative laboratory values between the groups. Adherence to study protocol is evident when viewing the individual Hb measurements and percentage of patients in the Hb range at certain time points. Complete blinding regarding the transfusion was not possible due to the study setup, but as mentioned before, clinicians were blinded to the ROTEM measurements. There are also several limitations to this study: between the groups, there is some difference in age and EuroSCORE values, and cell salvage was not regularly used. Most importantly, the authors were unable to reach the lower transfusion threshold in the majority of patients as lowest mean Hb values in both groups remained closer to 90 g/L. Power was calculated with suggested reduction of 25% in bleeding based on the authors' previous study, but effective mean blood loss was only about half of the previous study.

Conclusion

This study showed no significant effect of transfusion thresholds of Hb 80 g/L and 100 g/L in terms of bleeding and ROTEM coagulation parameters. It also seems that there might not be any difference considering safety of the 2 different thresholds. Less transfusion means less risk of transfusion-related adverse events and cost savings. Further studies to clarify optimal Hb threshold in cardiac surgery are needed.

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References

- 1 Roeloffzen WWH, Kluin-Nelemans HC, Bosman L, et al. Effects of red blood cells on hemostasis. *Transfusion* 2010;50:1536–44.
- 2 Murphy GJ, Reeves BC, Rogers CA, et al. Increased mortality, post-operative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. *Circulation* 2007;116:2544–52.
- 3 Karkouti K, Wijeyesundera DN, Beattie WS. Risk associated with preoperative anemia in cardiac surgery: A multicenter cohort study. *Circulation* 2008;117:478–84.
- 4 Esper AS, Subramaniam K, Tanaka KA. Pathophysiology of cardiopulmonary bypass: Current strategies for the prevention and treatment of anemia, coagulopathy, and organ dysfunction. *Semin Cardiothorac Vasc Anesth* 2014;18:161–76.
- 5 Bennett-Guerrero E, Zhao Y, O'Brien SM, et al. Variation in use of blood transfusion in coronary artery bypass graft surgery. *JAMA* 2010;304:1568–75.

- 6 Horvath KA, Acker MA, Chang H, et al. Blood transfusion and infection after cardiac surgery. *Ann Thorac Surg* 2013;95:2194–201.
- 7 Freeland K, Hamidian Jahromi A, Duvall L, et al. Postoperative blood transfusion is an independent predictor of acute kidney injury in cardiac surgery patients. *J Nephropathol* 2015;4:121–6.
- 8 Shaw RE, Johnson CK, Ferrari G, et al. Blood transfusion in cardiac surgery does increase the risk of 5-year mortality: Results from a contemporary series of 1714 propensity-matched patients. *Transfusion* 2013;54:1106–13.
- 9 Carson JL, Guyatt G, Heddle NM, et al. Clinical practice guidelines from the AABB. *JAMA* 2016;316:2025–35.
- 10 Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *NEJM* 1999;340:409–17.
- 11 Holst LB, Haase N, Wetterslev J, et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. *NEJM* 2014;371:1381–91.
- 12 Curley GF, Shehata N, Mazer CD, et al. Transfusion triggers for guiding RBC transfusion for cardiovascular surgery. *Crit Care Med* 2014;42:2611–24.
- 13 Murphy GJ, Pike K, Rogers CA, et al. Liberal or restrictive transfusion after cardiac surgery. *NEJM* 2015;372:997–1008.
- 14 Reeves BC, Pike K, Rogers CA, et al. A multicentre randomised controlled trial of transfusion indication threshold reduction on transfusion rates, morbidity and health-care resource use following cardiac surgery (tiTRe2). *Health Technol Assess* 2016;20:1–260.
- 15 Ouaknine-Orlando B, Samam CM, Riou B, et al. Role of the hematocrit in a rabbit model of arterial thrombosis and bleeding. *Anesth* 1999;90:1454–61.
- 16 Olde Engberink RHG, Kuiper GJAJM, Wetzels RJH, et al. Rapid and correct prediction of thrombocytopenia and hypofibrinogenemia with rotational thromboelastometry in cardiac surgery. *J Cardiothorac Vasc Anesth* 2014;28:210–6.
- 17 Reinhöfer M, Brauer M, Franke U, et al. The value of rotation thromboelastometry to monitor disturbed perioperative haemostasis and bleeding risk in patients with cardiopulmonary bypass. *Blood Coag Fibrinolysis* 2008;19:212–9.
- 18 Bolliger D, Tanaka KA. Roles of thrombelastography and thromboelastometry for patient blood management in cardiac surgery. *Transfusion Med Rev* 2013;27:213–20.
- 19 Roques F, Nashef SA, Michel P, et al. Risk factors and outcome in European cardiac surgery: Analysis of the EuroSCORE multinational database of 19030 patients. *Eur J Cardiothorac Surg* 1999;15:816–23.
- 20 Schramko AA, Suojäranta-Ylinen RT, Kuitunen AH, et al. Rapidly degradable hydroxyethyl starch solutions impair blood coagulation after cardiac surgery: A prospective randomized trial. *Anesth Analg* 2009;108:30–6.
- 21 Schramko AA, Suojäranta-Ylinen RT, Kuitunen AH, et al. Hydroxyethylstarch and gelatin solutions impair blood coagulation after cardiac surgery: A prospective randomized trial. *Br J Anaesth* 2010;104:691–7.
- 22 Lindroos A-C, Schramko AA, Niiya T, et al. Effects of combined balanced colloid and crystalloid on rotational thromboelastometry in vitro. *Perfusion* 2011;26:422–7.
- 23 Undas A, Stepień P, Branicka A, et al. Thrombin formation and platelet activation at the site of vascular injury in patients with coronary artery disease treated with clopidogrel combined with aspirin. *Kardiologia Pol* 2009;67:591–8.
- 24 Iselin BM, Willmann PF, Seifert B, et al. Isolated reduction of haematocrit does not compromise in vitro blood coagulation. *Br J Anaesth* 2001;87:246–9.
- 25 Spiezia L, Radu C, Marchioro P, et al. Peculiar whole blood rotation thromboelastometry (Rotem) profile in 40 sideropenic anaemia patients. *Thromb Haemost* 2008;100:1106–10.
- 26 Petäjä L, Røsjø H, Mildh L, et al. Predictive value of high-sensitivity troponin T in addition to EuroSCORE II in cardiac surgery. *Interact CardioVasc Thorac Surg* 2016;23:133–41.
- 27 Cloin E, Noyez L. Changing profile of elderly patients undergoing coronary bypass surgery. *Neth Heart J* 2005;13:132–8.